IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHIESI USA, INC., CORNERSTONE BIOPHARMA, INC., and EKR THERAPEUTICS, LLC, Plaintiffs, v. EXELA PHARMA SCIENCES LLC, EXELA PHARMSCI, INC., and EXELA HOLDINGS, INC., Defendants.	Civil Action No. 1:13-cv-01275-GMS [redacted]

PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

Francis DiGiovanni
DRINKER BIDDLE & REATH LLP
222 Delaware Avenue
Suite 1410
Wilmington, DE 19801-1621
Telephone No.: (302) 467-4200
Facsimile No.: (302) 467-4201

Edgar H. Haug
Angus Chen
Nicholas F. Giove
Leann M. Clymer
Michael W. Harkness
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
Telephone No.: (212) 588-0800
Facsimile No.: (212) 588-0500
Attorneys for Plaintiffs
Chiesi USA, Inc.,
Cornerstone BioPharma, Inc.,
and EKR Therapeutics, LLC

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I. INTRODUCTION

Plaintiffs Cornerstone Therapeutics Inc. (n/k/a Chiesi USA, Inc.), Cornerstone BioPharma, Inc., and EKR Therapeutics, LLC (collectively, "Chiesi" or "Plaintiffs") submit this brief in support of their proposed constructions for the disputed claim terms of the four patents-in-suit, U.S. Patent Nos. 7,612,102 ("the '102 patent"), 7,659,290 ("the '290 patent"), 7,659,291 ("the '291 patent"), and 8,455,524 ("the '524 patent") (collectively, the "patents-in-suit").[1]

Chiesi's constructions are consistent with the context of the claims and aligned with the intrinsic record. They comport with the ordinary meaning of the terms as understood by a Person of Ordinary Skill in the Art at the time of the invention ("POSA") in view of the claims, specifications, and prosecution histories. Chiesi's constructions are supported by the expert declaration of Alexander M. Klibanov, Ph.D. (pharmaceutical formulation), who confirms that Chiesi's constructions are consistent with how a POSA would understand the disputed terms.[2]

Defendants Exela Pharma Sciences LLC, Exela PharmSci, Inc., and Exela Holdings, Inc. (collectively, "Exela" or "Defendants"), on the other hand, propose constructions that are inconsistent with the intrinsic and extrinsic evidence in order to manufacture baseless invalidity and noninfringement defenses. For example, Exela's construction of "a pre-mixed aqueous solution" is divorced from and inconsistent with the intrinsic record because it encompasses prior art dosage forms that the patentee repeatedly and expressly disclaimed during prosecution of the patents-in-suit. And Exela's constructions of the "buffer" terms (i) erroneously require that a "buffer" be "separate and distinct" from the other components of the claimed formulations, directly contradicting the patents-in-suit and the universally acknowledged principle that

[1] JA Exs. A–D. "JA Ex. __" refers to Exhibits in the Joint Appendix of Intrinsic Evidence. "Ex. __" refers to Exhibits to the *Declaration of Angus Chen, Esq.* filed herewith.

[2] The declaration of Dr. Klibanov, filed herewith, is referenced as "Klibanov ¶ __."

components of pharmaceutical formulations frequently serve multiple purposes; and (ii) commit the cardinal sin of importing the limitation "throughout the shelf-life" from the specifications.

Exela's litigation-driven definitions should be rejected, and the Court should adopt Chiesi's proposed claim constructions in their entirety.

II. BACKGROUND OF THE INVENTION

This is a Hatch-Waxman action arising from Exela's filing of a Supplemental New Drug Application under 21 U.S.C. § 505(b)(2) seeking FDA approval to market generic nicardipine hydrochloride pre-mixed ready-to-use injectable drug products containing 0.1 mg/mL and 0.2 mg/mL nicardipine hydrochloride in 0.9% sodium chloride. The claims of the patents-in-suit cover Chiesi's Cardene® I.V. Premixed Injection—a pre-mixed ready-to-use nicardipine hydrochloride injectable drug product. (JA Ex. A, '102 pat., col.1 ll.16-18; col.10 ll.25-27).[3]

The claimed pre-mixed ready-to-use nicardipine compositions solve a number of problems associated with non-ready-to-use (e.g., concentrated) nicardipine injectable products, which are supplied as a concentrated solution stored in glass ampuls that require dilution by medical personnel prior to administration to a patient.[4] (*Id.,* col.1 ll.23-26). A dosage form that requires the additional step of mixing the drug with diluents(s) prior to administration is known as a point-of-care dosage form. (Ex. 1, Bates, at 152). Premixed ready-to-use ("RTU") and point-of-care ("POC") formulations are fundamentally different dosage forms. (Ex. 2, Ruble, at 34). "Premixed products generally involve an absolutely RTU container of medication … [whereas a] POC product's container may use an isolation technology that separates the drug and diluents until administration." (*Id.*).

[3] The patents-in-suit share substantially the same specification. For convenience, citation to the specifications of the patents-in-suit are to the '102 patent.

[4] Concentrated, injectable nicardipine was marketed under the name Cardene® I.V.—a different product than the claimed pre-mixed ready-to-use Cardene® I.V. ***Premixed Injection***.

Diluting point-of-care nicardipine ampul dosage forms "is associated with a number of disadvantages." (JA Ex. A, '102 pat., col.1 ll.40-42). *First*, after dilution of the point-of-care nicardipine ampul product, "the diluted solution is only stable for 24 hours at room temperature." (*Id.*). *Second*, "the pH of the diluted formulation varies depending on the choice of diluent." (*Id.*, col.1 ll.42-43). *Third*, when using point-of-care nicardipine "under emergency conditions to control blood pressure, dilution of the concentrated ampul formulation consumes valuable time that could be used to treat a patient." (*Id.,* col.1 ll.44-47). *Fourth*, there is risk of "contamination, dosage errors, and safety hazards associated with the use of glass ampuls." (*Id.,* col.1 ll.47–50; *see also* JA Ex. H, Brittain Decl. at A-152–3).

A pre-mixed ready-to-use nicardipine product overcomes the disadvantages associated with a point-of-care nicardipine ampul dosage form. (*Id.*, col.1 ll.51-52; *see also* JA Ex. H, Brittain Decl. at A-152–3). In particular:

> The ready-to-use, injectable formulations described herein [in the patents-in-suit] are stable, allow medical personnel[sp] to use prepared containers containing an injectable formulation off the shelf without additional preparation [e.g., dilution], avoid potential contamination problems, and eliminate dosage errors.

(*Id.*, col.1 ll.52-56). As a result, the claimed pre-mixed compositions are more convenient, stable at room temperature, easier to administer, reduce medical waste, and safer than a point-of-care dosage form, particularly during time-critical emergencies. (*Id.*, col.1 ll.61-col.2 l.9).

III. GENERAL CLAIM CONSTRUCTION PRINCIPLES

Claim construction is a matter of law that is determined by the court. *Teva Pharm. USA, Inc. v. Sandoz, Inc*., 135 S. Ct. 831, 836 (2015). Claim terms must be given "the meaning that the term would have been given to a [POSA] in question at the time of invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). Ordinary meaning may be derived from a variety of sources, both intrinsic (*e.g.*, claims, specifications, and prosecution histories) and

extrinsic (e.g., dictionaries, treatises, and expert testimony) to the patents-in-suit. *Teleflex, Inc. v. Ficosa North Am. Corp*., 299 F.3d 1313, 1324-25 (Fed. Cir. 2002).

"[T]he complete record of the proceedings before the PTO"—the prosecution history—should be considered to elucidate the meaning of a disputed claim term. *Phillips*, 415 F.3d at 1317. It "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention." *Id.* "The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution.'" *Chimie v. PPG Indus., Inc*., 402 F.3d 1371, 1384 (Fed. Cir. 2005) (*quoting ZMI Corp. v. Cardiac Resuscitator Corp*., 844 F.2d 1576, 1580 (Fed. Cir. 1988)). "[W]here the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." *Omega Eng'g, Inc. v. Raytek Corp*., 334 F.3d 1314, 1324 (Fed. Cir. 2003). Under this doctrine, courts "cannot construe the claims to cover subject matter broader than that which the patentee itself regarded as comprising its inventions and represented to the PTO." *Microsoft Corp. v. Multi-Tech Sys.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004).

Extrinsic evidence such as dictionaries, treatises, and expert testimony may also be helpful in construing patent claims, but must always be "considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1317–19. The Supreme Court recently held that the review of extrinsic evidence, such as expert opinions, is a factual finding subject to "clear error review." *Teva Pharm. USA, Inc*., 135 S. Ct. at 836-9.

In sum, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, at 1316 (citation omitted).

IV. CHIESI'S PROPOSED CONSTRUCTIONS ADHERE TO WELL ESTABLISHED CLAIM CONSTRUCTION PRINCIPLES AND SHOULD BE ADOPTED

A. The "Pre-mixed Aqueous Solution" Claim Term Should Be Construed to Mean Ready-to-Use Pharmaceutical Compositions

Claim Term	Chiesi's Proposed Construction	Exela's Proposed Construction
a pre-mixed aqueous solution	a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors	An aqueous solution that does not require reconstitution or dilution before administration to a patient.

Chiesi's construction is supported by the intrinsic evidence, and, in fact, is based on language from the specifications of the patents-in-suit:

Chiesi's Proposed Construction	Corresponding Portions of the Specifications
a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors	the term "pre-mixed", as used herein, means a ***pharmaceutical composition that is already mixed from the point of manufacture*** and does not require dilution or further processing before administration. * * * the ***ready-to-use***, injectable formulations described herein are ***stable, allow medical personnel[sp] to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoid potential contamination problems, and eliminate dosage errors***. (JA Ex. A, '102 pat., col.11 ll.25-29, col.1 ll.52-57) (emphasis added).

1. The Claimed "Pre-Mixed" Compositions Are "Ready-To-Use"

The patents-in-suit claim improvements over point-of-care nicardipine hydrochloride dosage forms that are stored in glass ampul containers and require reconstitution or dilution

before administration to a patient. (*Supra*, Sec. II). The specifications of the patents-in-suit characterize the claimed compositions as "ready-to-use" with no reconstitution or dilution required, and Exela concedes (ECF No. 48-1, at 1) that the claimed "pre-mixed" inventions "do[] not require reconstitution or dilution." (*See, e.g.*, JA Ex. A, '102 pat., col.1 ll.51-67, col.2 ll.20-21, col.3 ll.10-12, col.11 ll.13-29). Thus, a POSA would have understood that "a pre-mixed aqueous solution" refers to a ready-to-use pharmaceutical composition. (Klibanov ¶ 24).

Further, the specifications ***contrast*** the claimed pre-mixed ready-to-use compositions from concentrated point-of-care compositions that require dilution and mixing after the point of manufacture. In particular, the patents-in-suit state:

> As used herein, the term "pre-mixed" refers to a pharmaceutical composition that does not require reconstitution or dilution before administration to a patient. ***In contrast to ampul formulations*** comprising nicardipine hydrochloride that must be diluted prior to use in a diluent and container selected by hospital personnel . . .

(JA Ex. A, '102 pat., col.3 ll.10-15 (emphasis added)). A POSA would not understand "a pre-mixed aqueous solution" to include point-of-care dosage forms such as concentrated ampul products. (Klibanov ¶¶ 24-25, 28-32). The specifications unequivocally distinguish the claimed pre-mixed ready-to-use compositions and their benefits from point-of-care dosage forms and their disadvantages. (JA Ex. A, '102 pat., col.1 ll.51-57, col.2 ll.4-9).

2. The Claimed Compositions Are "Already Mixed from the Point of Manufacture"

The intrinsic and extrinsic evidence confirms that the claimed "pre-mixed" compositions are "already mixed from the point of manufacture" as set forth in Chiesi's proposed construction.

As explained above, the patents-in-suit expressly state that the claimed "pre-mixed" compositions are, *inter alia*, "***already mixed from the point of manufacture*** and do[] not require dilution or further processing before administration." (JA Ex. A, '102 pat., col.11 ll.25-29 (emphasis added)). And the specifications describe that the claimed pre-mixed compositions are

made so that they are "'dispensed in pharmaceutically acceptable containers for storage and direct administration to patients.'" (Klibanov ¶ 26) (*quoting* JA Ex. A, '102 pat., col.2 ll.28-37). Thus, the intrinsic record confirms that the claimed compositions are mixed from the point of manufacture and require no further manipulation. (Klibanov ¶¶ 24-32; JA Ex. G, July 6, 2009, Amendment, at A-142–3; JA Ex. H, Brittain Decl., at A-152–3).

A POSA would ***not*** consider a nicardipine hydrochloride solution prepared (i.e., mixed and/or diluted) ***after*** the point of manufacture in a pharmacy, hospital or otherwise to be encompassed by the meaning of a "pre-mixed aqueous solution." Rather, a POSA would understand that "pre-mixed" refers to "[m]anufacturer-[p]repared" nicardipine injectable solutions that are ready-to-use for direct administration off the shelf—not a point-of-care dosage form that requires additional mixing steps after manufacture but prior to administration. (Klibanov ¶¶ 26, 29, 31, 34-35; Ex. 1, Bates, at 152). Thus, the claimed "pre-mixed" compositions are already mixed from the point of manufacture and a construction of "a pre-mixed aqueous solution" cannot include mixing by medical personnel ***after*** the point of manufacture and ***before*** administration to a patient. (Klibanov ¶¶ 23-35).

3. The Claimed Compositions Are "Stable" and Avoid "Potential Contamination Problems" and "Dosage Errors"

The specifications and prosecution histories of the patents-in-suit also confirm that the claimed "pre-mixed aqueous solution[s]" are stable (i.e., "remain[] in a state or condition that is suitable for administration to a patient") and avoid both contamination problems and dosing errors. (JA Ex. A, '102 pat., col.3 ll.53-55).

For example, the specifications repeatedly emphasize that the claimed formulations are "stable" for "at least 24 months." (*See, e.g.*, JA Ex. A, '102 pat., col.8 ll.33-44; col.3 ll.46-49; Klibanov ¶ 27). The specifications also state that the claimed pre-mixed, ready-to-use

compositions "eliminate dosage errors." (JA Ex. A, '102 pat., col.1 ll.52-57; Klibanov ¶ 23). And the prosecution histories espouse the safety, stability, and ease-of-use advantages of the claimed pre-mixed ready-to-use compositions over point-of-care ampul dosage forms. (Klibanov ¶¶ 31-32). The provisional application and prosecution histories of the patents-in-suit explain that the claimed compositions are "***safer*** for patients because they reduce or eliminate microbiological contamination that may occur during dilution" of a point-of-care dosage form. (JA Ex. E, '074 Appl., at A-95–7 (emphasis added); JA Ex. G, July 6, 2009, Amendment, at A-142–3; JA Ex. H, Brittain Decl., at A-152–3; *see also* Klibanov ¶ 30).

4. The Patentee Explicitly Disclaimed "Point-of-Care" Dosage Forms During Prosecution

As shown in the table below, not only does Chiesi's construction have direct support from the specification, but each component of Chiesi's construction is based on a corresponding statement in the specification or prosecution history distinguishing the "pre-mixed" inventions from the disclaimed ampul and diluted dosage forms (and their disadvantages):

Chiesi's Proposed Construction	The Patentees' Disclaimer in the Prosecution History
"a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and	"Applicant described the ***prior art teachings*** are directed toward the ***concentrated*** form of nicardipine, which ***is not the same as the premixed formulation*** presented in the claims. The stability of ***the premixed formulation*** was discussed as an improvement ***over*** previous ***diluted samples of the prior art concentrate***." (JA Ex. F, June 16, 2009, Examiner Interview Summary Record, at A-134) (emphasis added). "The McFarlane reference describes a nicardipine hydrochloride concentrated formulation that requires reconstitution prior to administration. By contrast, I note that ***the ready-to-use aqueous nicardipine hydrochloride formulation of the present invention does not require reconstitution*** and is indicated to be stable for an extended period of time." (JA Ex. H, Brittain Decl., at A-152–3) (emphasis added).

Chiesi's Proposed Construction	The Patentees' Disclaimer in the Prosecution History
is stable,	"The diluted [point-of-care] form must be discarded in 24 hours due to ***stability issues***." (JA Ex. G, July 6, 2009, Amendment, at A-143) (emphasis added).
allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation,	"The requirement of dilution [for the point-of-care form] can result in a ***lag time*** that prevents a patient in an acute setting from receiving the drug in a timely fashion." (*Id.*, at A-142) (emphasis added).
avoids potential contamination problems,	"The breaking of the ampule neck [for the point-of-care form] may result in exposing the patient to glass ***contamination of the product*** and exposing health care professionals to an increased risk of injuring themselves when handling and breaking the glass ampules." (*Id.*) (emphasis added).
and eliminates dosage errors"	"There is an increased probability of ***dosing errors*** [for the point-of-care form] by requiring health care professionals to dilute the product. Such errors may manifest themselves as an overdose or an underdose if the product is not diluted properly. Likewise, there is an additional probability that the concentrated form will be administered "as is" which is contraindicated and can result in adverse events." (*Id.*) (emphasis added).

Under the doctrine of prosecution history disclaimer, courts "cannot construe the claims to cover subject matter broader than that which the patentee itself regarded as comprising its inventions and represented to the PTO." *Microsoft*, 357 F.3d at 1349. "[W]here the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." *Omega Eng'g,* 334 F.3d at 1324. Prosecution history disclaimer is particularly relevant when, as here, a patentee "argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection." *Seachange Int'l, Inc. v. C-COR Inc*., 413 F.3d 1361, 1372-73 (Fed. Cir. 2005). The patentee's argument "may serve to narrow the scope of otherwise broad claim language." *Id.; see also Rheox, Inc. v. Entact, Inc*., 276 F.3d 1319,

1325 (Fed. Cir. 2002) ("Explicit arguments made during prosecution to overcome prior art can lead to narrow claim interpretations …."); *Ekchian v. Home Depot, Inc*., 104 F.3d 1299, 1304 (Fed. Cir. 1997) ("Since, by distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, he is by implication surrendering such protection."). Criticizing disadvantages of a prior art product that lacks the claimed features "operates as a clear disavowal" of the prior art product. *Astrazeneca AB v. Mut. Pharm. Co*., 384 F.3d 1333, 1340 (Fed. Cir. 2004); *Kinik Co. v. Int'l Trade Comm'n*, 362 F.3d 1359, 1365 (Fed. Cir. 2004).

The Federal Circuit routinely bases the construction of disputed claim language on prosecution history statements that distinguish the claimed invention from and criticize the prior art. *See, e.g., MBO Labs., Inc. v. Becton, Dickinson & Co*., 474 F.3d 1323, 1329-30 (Fed. Cir. 2007). *MBO* concerned a patent directed to safety needles with a guard to cover the needle's tip once it is removed from a patient. *Id*. at 1326. The district court construed the disputed term "immediately" to require the activation of the safety guard simultaneously with removal from the patient. *Id*. at 1329. The Federal Circuit affirmed and observed that during prosecution MBO "distinguished its invention from and criticized the [prior art]" by arguing that "the MBO invention, in contrast to [the prior art], does provide assurance that the needle will be made instantly safe upon withdrawal from the patient." *Id*. at 1330. Such "arguments . . . are useful for determining whether the patentee intended to surrender territory, since they indicate in the inventor's own words ***what the invention is not***." *Id*. (emphasis added) (citation omitted).

Here, as in *MBO*, the intrinsic evidence confirms that Chiesi's claimed invention is ***not*** a point-of-care dosage form. *First*, the specifications explicitly describe "pre-mixed" as a ready-to-use formulation that does not require reconstitution or dilution before administration, which is "***in contrast to ampul formulations***" that do require reconstitution or dilution before

administration. (*See* JA Ex. A, '102 pat., col.3 ll.10-15 (emphasis added); *see also* col.11 ll.25-40). *Second*, during prosecution, the patentee described problems with point-of-care ampul nicardipine products (such as "stability issues," "lag time that prevents a patient . . . from receiving the drug in a timely fashion," "contamination," and "dosing errors") that were solved by the "storage stable, ready-to-use nicardipine hydrochloride intravenous product [of] the present invention." (*See* JA Ex. G, July 6, 2009, Amendment, pp 8-9).[5] *Third*, the patentee filed with the Patent and Trademark Office an expert declaration that enumerated the advantages of the pre-mixed ready-to-use inventions over point-of-care nicardipine products and their associated problems. (*See* JA Ex. H, Brittain Decl., A-152–3). *Fourth*, after the Examiner was presented at an interview with physical samples of both the claimed pre-mixed ready-to-use nicardipine compositions and the point-of-care nicardipine product, he stated:

> Applicant described the ***prior art teachings*** are directed toward the ***concentrated*** form of nicardipine, which ***is not the same as the premixed formulation*** presented in the claims. The stability of ***the premixed formulation*** was discussed as an improvement over previous ***diluted samples of the prior art concentrate***.

(JA Ex. F, June 16, 2009, Examiner Interview Summary Record, at A-134).

The intrinsic evidence, including the prosecution histories, thus confirms that "the patentee [] unequivocally disavowed [diluted or reconstituted point-of-care products] to obtain his patent" by explicitly stating that point-of-care products are "***not the same***" as the claimed "pre-mixed" inventions. *Omega Eng'g,* 334 F.3d at 1324. In doing so, the patentee clearly "indicat[ed] what the claims do not cover." *Ekchian*, 104 F.3d at 1304. Chiesi's construction

[5] The patents-in-suit are all children of the application that issued as the '102 patent. "[P]rosecution disclaimer may arise from disavowals made during the prosecution of ancestor patent applications." *Omega Eng'g., Inc*., 334 F.3d at 1333 (quoting *Advanced Cardiovascular Sys., Inc. v. Medtronic, Inc*., 265 F.3d 1294, 1305 (Fed. Cir. 2001)).

properly defines the claim term according to what "the patentee itself regarded as comprising its inventions and represented to the PTO" during prosecution. *Microsoft Corp.*, 357 F.3d at 1349.

Exela's construction is wrong because it (i) is broad enough to include point-of-care dosage forms, such as a diluted concentrate form of nicardipine, and (ii) renders other expressly recited claim language superfluous.

First, Exela's construction is overly broad because it does not exclude a dosage form that is reconstituted/diluted ***after*** the point of manufacture but before administration (e.g., in a pharmacy).[6] Indeed, during the parties' meet-and-confer, Exela asserted that the patents' definition of "pre-mixed" in column 11 that defines the term as "a pharmaceutical composition that is already mixed from the point of manufacture" is ***not*** a claimed "pre-mixed" embodiment. (Chen Decl. ¶ 10). Thus, Exela's construction is divorced from and inconsistent with the intrinsic record because it encompasses point-of-care dosage forms (and in particular, a diluted concentrate form)—subject matter that the patentee repeatedly and expressly disclaimed. A construction that attempts to "construe the claims to cover subject matter broader than that which the patentee itself regarded as comprising its inventions" is wrong as a matter of law. *Microsoft*, 357 F.3d at 1349. Exela's litigation-driven construction that attempts to manufacture an invalidity defense should be rejected. Chiesi's construction properly defines "a pre-mixed aqueous solution" as, *inter alia*, already mixed at the point of manufacture and excludes point-of-care dosage forms that are diluted after manufacture. (*See supra* Sec. IV.A.2).

[6] Defendants in a related action have also improperly argued that the same disclosure from the patents-in-suit that Exela relies on for its construction ("does not require reconstitution or dilution before administration to a patient") expressly encompasses point-of-care dosage forms because such dosage forms may be reconstituted/diluted in a pharmacy (after the point of manufacture) yet allegedly are still "pre-mixed." (Ex. 8, Portions of Sandoz's Opening Brief at 9-13, *Chiesi USA, Inc., et al., v. Sandoz Inc., et al*., CA No. 1:13-cv-05723-NLH-AMD (D.N.J. Nov. 26, 2014)).

Second, Exela's construction is wrong as a matter of law because it renders superfluous a phrase that appears in certain independent claims of the patents-in-suit. Specifically, the phrase "wherein the aqueous solution ***requires no dilution before administration***"—which is recited in claims 1 and 2 of the '524 patent—would become superfluous under Exela's proposed construction of the term "a pre-mixed aqueous solution": "an aqueous solution that ***does not require*** reconstitution or ***dilution before administration*** to a patient."[7] The Federal Circuit has "reinforced the importance of construing claim terms . . . such that words in a claim are not rendered superfluous." *Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270, 1275 (Fed. Cir. 2012). Exela's construction should be rejected because it is contrary to the well-established rule that "claims are interpreted with an eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005).

Chiesi's proposed constructions—wholly supported by the intrinsic and extrinsic evidence—should be adopted. The Court's construction should at a minimum exclude point-of-care dosage forms, including concentrated ampul dosage forms and diluted forms thereof. *See* Ex. 3, *Markman* Order at 2-5, *Salix Pharms., Inc. v. Lupin Ltd.,* No. 12-1104 (D. Del., Dec. 17, 2013) (citing *Omega Eng'g, Inc*., 334 F.3d at 1325) (after determining patentee disclaimed pH-sensitive enteric polymers during prosecution, construing "matrix-forming polymer" to mean "polymers, *except* pH-sensitive enteric polymers, that are used to form the non gel-forming polymer matrix." (emphasis added)). The inventors made clear that the claims of the patents-in-suit cover a "pre-mixed aqueous solution," not point-of-care dosage forms or diluted point-of-care dosage forms. *MBO Labs., Inc*., 474 F.3d at 1330 ("Prosecution arguments . . . are useful

[7] The term "a pre-mixed aqueous solution" is also recited in claims 1 and 2 of the '524 patent. (JA Ex. D, '524 pat., claims 1 and 2).

for determining whether the patentee intended to surrender territory, since they indicate in the inventor's own words what the invention is not.").

B. The Patents-In-Suit Describe Full-Term Stability Measurements for the "Room Temperature" Claim Terms

Claim Term	Chiesi's Proposed Construction	Exela's Proposed Construction
one year or three months "at room temperature"	one year or three months "full-term at room temperature"	No construction necessary.

A POSA would understand the claim terms one year or three months "at room temperature" to mean one year or three months "full-term at room temperature" in the context of the intrinsic and extrinsic record. (Klibanov ¶¶ 38-43).

The intrinsic evidence supports Chiesi's constructions and confirms that the claimed limitations referring to potency and stability[8] must be based on full-term data. (Klibanov ¶¶ 39-43). For example, the specifications cite a reference that emphasizes hypothesized drug product stability "should be confirmed with ***full-term***, normal studies." (JA Ex. A, '102 pat., col.15 ll.7-9; JA Ex. I, *The Chemical Stability of Pharmaceuticals*, at A-174 (emphasis added); Klibanov ¶ 43). This reference is intrinsic evidence because "prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence." *V-Formation, Inc. v. Benetton Grp. SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005) (citation omitted). Thus, a POSA would understand from the patents-in-suit that one year or three months "at room temperature" means one year or three months "***full-term*** at room temperature." (Klibanov ¶¶ 39-43).

[8] The one year or three months "at room temperature" terms refer to conditions under which the claimed compositions exhibit (i) a "less than 10% decrease in the concentration of nicardipine hydrochloride" (i.e., drug potency) and (ii) a "total impurity formation of less than about 3%." (*See, e.g.*, JA Ex. A, '102 pat., claim 1; JA Ex. C, '291 patent, claim 1; Klibanov ¶ 38).

Chiesi's constructions are consistent with the claims of the patents-in-suit, which repeatedly and consistently refer to periods of time that meet or ***exceed*** the full-term of one year or three months. For example, claim 1 of the '102 patent recites:

> the aqueous solution when stored in the container for ***at least*** one year at room temperature exhibiting (i) less than a 10% decrease in the concentration of nicardipine hydrochloride and (ii) a total impurity formation of less than about 3%.

(emphasis added). Similarly, claim 1 of the '291 patent recites "the composition when stored in container for ***at least*** three months at room temperature . . . ." (emphasis added). Because the words "***at least***" precede these disputed terms, a POSA would understand the terms as describing data measured from a period of ***at least*** one year or three months at room temperature, i.e., one year or three months full-term at room temperature. (Klibanov ¶¶ 39-43).

Further, the specifications of the patents-in-suit indicate that the claimed compositions are stable at room temperature for ***at least*** one year:

> [T]hese pharmaceutical compositions are ***stable at room temperature for at least one year***. When stored at room temperature, the pharmaceutical compositions exhibit between 0% to about 15% loss of drug and between 0% to about 3% (w/w) total impurity formation ***over an eighteen to twenty four month period***.

(JA Ex. A, '102 pat., col.1 l.65–col.2 l.3 (emphasis added); *see also* col.3 ll.43-48; Klibanov ¶ 41). Thus, a POSA would understand these disputed terms to refer to the ***full-term*** of one year or three months. (Klibanov ¶¶ 39-43).

Exela has refused to provide any proposed construction for one year or three months "at room temperature." (ECF No. 48-1 at 3). But "[a] determination that a claim term 'needs no construction' or has the 'plain and ordinary meaning' may be inadequate . . . when reliance on a term's 'ordinary' meaning does not resolve the parties' dispute." *O2 Micro Int'l. Ltd. v. Beyond Innovation Tech. Co., Ltd*., 521 F.3d 1351, 1361 (Fed. Cir. 2008); *see also NuVasive, Inc. v. Globus Med., Inc.*, No. 10-849 2013 WL 3705731, at *3 (D. Del. July 12, 2013).

Chiesi's constructions should be adopted because they are supported by the intrinsic evidence, and "align[] with the patent's description of the invention . . . ." *Phillips* at 1316.

C. The "Buffer" Claim Terms Should be Defined as a System Capable of Maintaining the pH of the Formulations

Claim Term	Chiesi's Proposed Constructions	Exela's Proposed Constructions
buffer	a system capable of maintaining the pH within an optimal pH range	Component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain an optimal pH range throughout the shelf-life of the product.
buffer in an amount to maintain pH from about 3.6 to about 4.7	a system capable of maintaining the pH within an optimal pH range in an amount to maintain pH from about 3.6 to about 4.7	Component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain a pH range from about 3.6 to about 4.7 throughout the shelf-life of the product.

1. Chiesi's Constructions Are Consistent with the Intrinsic Record

Chiesi's constructions are taken from the definition provided in the specifications of the patents-in-suit: "the premixed pharmaceutical compositions provided herein . . . inclu[de] a buffer ***capable of maintaining the pH within an optimal pH range***, which is typically between 3.6 to about 4.7." (JA Ex. A, '102 pat., col.3 ll.15-19; *see also* JA Ex. E, '074 Appl., at A-101).

Chiesi's constructions are consistent with the teachings of the patents-in-suit. For example, the specifications explain that pH levels of the formulation may have an impact on nicardipine concentration and impurity formation in the claimed inventions. (JA Ex. A, '102 pat., col.13 ll.33-35; col.15 ll.10-22). Example 2 of the patents-in-suit explains that "loss in product potency (decrease in % nicardipine drug remaining) due to degradation and adsorption

on to the bag surface increased as the formulation pH was increased" and that "as the pH was decreased, the total impurities increased." (JA Ex. A, '102 pat., col.13 ll.33-38). The specifications teach that loss of drug product potency caused by degradation and adsorption may be controlled by including "a buffer ***capable of maintaining the pH within an optimal pH range***." (JA Ex. A, '102 pat., col.3 ll.7-18). Based on these disclosures, a POSA would understand the importance of maintaining pH within an optimal range. (Klibanov ¶¶ 48-51).

Chiesi's constructions are consistent with the plain and ordinary meaning of "buffer" and naturally align with the disclosures of the patents-in-suit. *Phillips*, 415 F.3d at 1316.

2. Exela's Constructions Improperly Add and Import Limitations that Contradict Express Disclosures in the Claims and Specifications

Exela's constructions of the "buffer" terms—which require that the buffer (i) be "separate and distinct" from the other components of the formulations and (ii) maintain pH "throughout the shelf-life of the product"—violate well-established principles of claim construction. (ECF No. 48-1 at 6-7). They are a thinly veiled attempt to manufacture a baseless noninfringement defense by having this Court rewrite the claims and adopt an exceedingly and unjustified narrow definition of "buffer." But "courts can neither broaden nor narrow claims to give the patentee something different than what he has set forth." *Tex. Instruments, Inc. v. U.S. ITC*, 988 F.2d 1165, 1171 (Fed. Cir. 1993). Exela's litigation-driven constructions should be rejected.[9]

[9] This District rejected Exela's attempt to improperly add/import limitations to "a buffering agent" claim term in another case. *Cadence Pharms. Inc., v. Paddock Labs., Inc.,* 886 F. Supp. 2d 445, 456 (D. Del. 2012). In *Cadence*, the court rejected Exela's proposed construction ("a system comprising a weak acid and its conjugate base, or a weak base and its conjugate acid in an effective concentration to resist material changes in pH") because "nothing in the patent limits the scope of the claimed buffering agent to an 'effective concentration' or one that resists 'material changes in pH.'" *Id.* Further, Exela's construction in that case tellingly did ***not*** include the limitations that it seeks to add/import here, further demonstrating that Exela's construction here is ***not*** how a POSA would understand the "buffer" terms.

a. Exela Adds a "Separate and Distinct" Limitation that Has No Support and Contradicts the Intrinsic and Extrinsic Evidence

Exela's constructions add an additional limitation requiring that a buffer be "separate and distinct" from each of the "nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster" components. (ECF No. 48-1 at 6-7). But the patents-in-suit ***nowhere*** state or suggest that the buffer system must be "separate and distinct" from other formulation components. (Klibanov ¶ 53). And a POSA would understand that a component in the claimed formulations can perform more than one function. (Klibanov ¶¶ 46, 52-61). In fact, the specifications identify several specific components that may serve more than one purpose. Of particular relevance here, the patents-in-suit disclose (and repeatedly claim) "citric acid" as a suitable buffer:

> 12. The pharmaceutical composition for parenteral administration of claim 1, wherein the buffer is citric acid.

(*See e.g.,* JA Ex. A, '102 pat., claim 12; Klibanov ¶¶ 55-56). But the patents-in-suit ***also*** describe "citric acid" as a suitable "pH adjuster." (JA Ex. A, '102 pat., col.5 ll.22-32). And the specifications list "pharmaceutically acceptable salts and acids of" citrate (i.e., citric acid), acetate (i.e., acetic acid), phosphate (i.e., phosphoric acid), and carbonate (i.e., carbonic acid) as "[b]uffers suitable for use in the pharmaceutical compositions" ***as well as*** "pH adjusters." (Klibanov ¶¶ 55-56; JA Ex. A, '102 pat., col.4 ll.49-54, col.5 ll.22-40). Further, the provisional application to the patents-in-suit specifically explains that "[b]uffering agents are used to ***adjust the pH*** of the pharmaceutical compositions." (JA Ex. E, '074 Appl., at A-101 (emphasis added)).

A POSA would understand that components of pharmaceutical formulations may serve multiple purposes, e.g., a pH adjuster ***and*** a buffer. (Klibanov ¶¶ 53-61). Exela's construction is erroneous because it directly contradicts this principle and fails to align with the specific disclosures in the claims and specifications of the patents-in-suit. *Phillips,* 415 F.3d at 1316.

b. Exela Imports a "Shelf-Life" Limitation From a Specific Embodiment in the Specifications

Exela improperly imports the phrase "throughout the shelf-life of the product"—a phrase that is only associated with ***exemplary embodiments***—into its constructions of the "buffer" terms.[10] (ECF No. 48-1, at 6-7). In doing so, Exela commits "[o]ne of the cardinal sins of patent law [by] reading a limitation from the written description into the claims." *Phillips*, 415 F.3d at 1319-1320; *see also Kara Tech. Inc. v. Stamps.com Inc*., 582 F.3d 1341, 1348 (Fed. Cir. 2009) ("The claims, not specification embodiments, define the scope of patent protection. The patentee is entitled to the full scope of his claims, and we will not limit him to his preferred embodiment or import a limitation from the specification into the claims.").

Exela relies on an exemplary disclosure of a buffer system disclosed in the specifications that refers only to ***some examples*** of the claimed inventions:

> ***In some embodiments***, the premixed formulation comprises, in addition to nicardipine and/or its pharmaceutically acceptable salts, a buffer that has sufficient buffering capacity to maintain the desired pH range ***throughout the shelf-life of the product***.

(JA Ex. A, '102 pat., col.4 ll.20-24 (emphasis added)). Exela ignores numerous other disclosures that expressly do ***not*** require pH to be maintained throughout the shelf-life, but, for example, require maintaining drug potency and/or impurity formation (two limitations that may be adversely affected by pH changes) for ***only three months***. (*See, e.g.,* JA Ex. A, '102 pat., claims 8 and 9; Klibanov ¶ 62). As explained *supra* Section IV.A.3, the shelf-life (i.e. stability) of the

[10] Exela's proposed constructions also limit a "buffer" to a ***single*** "[c]omponent." (ECF No. 48-1 at 6-7). This contradicts the specifications and improperly narrows the plain meaning of the "buffer" terms. (Klibanov ¶¶ 52-56). The specifications explicitly state that "the compositions may comprise ***multiple*** buffering agents." (JA Ex. A, '102 pat., col.13 ll.28-30 (emphasis added)). And the Merriam-Webster Medical Desk Dictionary defines a "buffer" as "a substance or ***mixture of substances*** . . . ." (Klibanov ¶ 57). Thus, a POSA would understand that a "buffer" in the context of the patents-in-suit describes ***one or more*** components of the claimed formulations that maintain the pH within the optimal pH range. (Klibanov ¶¶ 44-61).

claimed inventions could be "***at least 24 months.***" (*See, e.g.*, JA Ex. A, '102 pat., col.8 ll.33-44 (emphasis added); *see also* col.3 ll.46-49; Klibanov ¶ 41). In fact, Chiesi's Cardene® I.V. Premixed Injection drug product has an FDA-approved shelf-life of twenty-four months, and [redacted]. (Ex. 5, Ordering Information, at 1; [redacted]). Thus, a POSA would understand that there is no requirement that the claimed inventions are limited to a buffer system that maintains pH levels "throughout the shelf-life of the product." (Klibanov ¶¶ 62-63).

* * *

In sum, Exela's constructions improperly add or import limitations into the claim terms that are not only inconsistent with the patents-in-suit, but also inconsistent with a POSA's understanding of "buffers." Exela's constructions are flawed and should be rejected.

V. CONCLUSION

Chiesi's constructions are (i) aligned with the intrinsic and extrinsic evidence; and (ii) supported by Chiesi's expert, who defines a POSA and construes the disputed terms from the perspective of a POSA. Exela's constructions, on the other hand, are inconsistent with the intrinsic and extrinsic evidence. Exela violates the doctrine of prosecution history disclaimer in attempting to improperly broaden "a pre-mixed aqueous solution" to cover diluted point-of-care dosage forms that the patentee unequivocally distinguished from the present inventions to obtain their patents. And Exela's constructions of the "buffer" claim terms (i) add limitations that contradict the patent specifications and conflict with a POSA's understanding of the plain meaning of the "buffer" terms; and (ii) inappropriately import examples from the specifications as limitations into the patent claims. Exela's definitions should be rejected and the Court should adopt Chiesi's proposed claim constructions in their entirety.

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s/ Francis DiGiovanni

Francis DiGiovanni (#3189)
DRINKER BIDDLE & REATH LLP
222 Delaware Avenue, Suite 1410
Wilmington, Delaware 19801
Telephone: (302) 467-4266
Facsimile: (302) 467-4201

Edgar H. Haug
Angus Chen
Nicholas F. Giove
Leann M. Clymer
Michael W. Harkness
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
Telephone No.: (212) 588-0800
Facsimile No.: (212) 588-0500

Attorneys for Plaintiffs
Chiesi USA, Inc.,
Cornerstone BioPharma, Inc.,
and EKR Therapeutics, LLC